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APPLICATION NO.	FILING DATE	NAME OF APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER	ART UNIT	PAPER NUMBER
KUNZ, G	183	8

ELAINE P. BRENNER
CORPORATE PATENT COUNSEL
ENZO BIOCHEM, INC.
60 EXECUTIVE BOULEVARD
FARMINGDALE, NY. 11735

DATE MAILED: 08/26/91

[illegible] copy of this communication to attorney in charge of prosecution
[illegible] PATENT AND TRADEMARKS

☒ This application has been examined ☒ Responsive to ~~communication~~ AMENDMENT B filed on 5/31/91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-51 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-51 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTOL-326 (Rev.9-89)

EXAMINER'S ACTION

In Amendment A filed May 31, 1991, Applicant's provisional election with traverse of Group I, claims 1 - 20 and 42 - 50, and further election of the methylphosphonate species defined by the new claim 51 is acknowledged. The restriction and election of species requirement was defined in the written restriction mailed April 1, 1991 (Paper No. 2).

After thorough consideration of the applicant's traversal of the restriction and election requirements, the examiner has rescinded all restriction and election requirements. An action on the merits of claims 1 - 51 is presented below.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 - 4, 8, 12 - 14, 19 - 23, 27 - 28, 31 - 33, and 38 - 51 are rejected under 35 U.S.C. § 102(b) as being anticipated by Miller et al. (Biochimie 67:769 - 776, 1985). Miller et al. discloses oligonucleotides possessing methylphosphonate linkages that inhibits the functioning of RNA. Oligomers possessing all or predominately all methylphosphonate groups read on the applicant's broad generic claims using functional language to define the oligomers.

Claims 1 - 4, 12 - 14, 19, 21 - 23, 31 - 33, 38, 41, and 42 - 50 are rejected under 35 U.S.C. § 102(b) as being anticipated by Matsukura et al. (PNAS 84: 7706-7710). Matsukura et al. discloses oligomers with phosphorothioate modified linkages. These oligomers were resistant to nuclease digestion and were able to inhibit the functioning of RNA.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 - 51 are rejected under 35 U.S.C. 103 as being unpatentable over Sarin et al. (PNAS 85:7448-7451) in view of Dash et al. (PNAS 84:7896-7900). Sarin et al. teaches that oligonucleotides possessing methylphosphonate linkages are biologically active and inhibit HIV expression. Furthermore, Sarin et al. teaches that oligomers possessing phosphorothioate, phosphoramidate, or methylphosphonate linkages

all possessed the ability to inhibit HIV.

Dash et al. disclose that complementary antisense oligomers promote the degradation of target mRNA molecules and that this inhibition is irreversible.

Consequently, it would have been obvious to the person of ordinary skill in the art at the time of the invention to make and use antisense oligomers possessing modified linkages known to be resistant to nucleases for the purpose of inhibiting a specific target RNA and further promoting its degradation by RNAse H. The need to optimize both the hybridization of an oligomer to a RNA sequence and its resistance to nucleases is well recognized by the art at the time of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description and failing to teach adequately how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is not enabling for all M's, N's, and B's defined by the generic claims. The breadth of the

claims is so great as to place an undue burden of experimentation upon the person of ordinary skill wanting to make and use the invention. There are hundreds of thousands of possible "modified nucleotides" that fall within the generic claims. However, the specifications exemplify one the methylphosphonate modification. The disclosure lacks guidance through the thousands of possibilities. While the applicant has provided RNAse and nuclease screening assays, the burden of making and the screening so many is undue. For instance, which modified bases confer endo- or exonuclease resistance at N, M or B?

In addition, the applicant has not documented that ethyl, propyl and butylphosphonates are not so bulky as to interfere with proper hybridization to the RNA and RNAse H activity as well. The bulkiness of these larger alkyl groups creates reasonable doubt that these potential RNA inhibitors will actually work.

Claims 1 - 51 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1 - 51 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 21 are so vague, indefinite, and confusing as to be nearly meaningless. The compound of claims 1 and 21 are termed a "modified nucleotide." It is not clear whether this is intended to mean an "oligonucleotide analog" or not. The three generic structures containing M, N, and B as variables are confusing. The claims are indefinite because the precise structure and attachment of these moieties to one another is not specified. Is N attached to M or B via the phosphodiester linkage or not? If N is attached to M or B via the phosphodiester linkage, is it through the 3'- or 5'-position? Both M and B are defined functionally instead of structurally. M is any nucleic acid that confers endonuclease resistance on the said "modified nucleotide." B is any moiety that confers exonuclease resistance to the terminus. Finally, the three generic formulas are vague because there is no indication which end is the 5'- and 3'-terminus.

Claim 3 continues the indefinite functional language by limiting the "modified nucleotide" to those capable of conferring RNAse sensitivity to the RNA.

Claim 7 is indefinite because it fails to define specifically the location of the methyl group(s) attached to the bases.

The following two indefinite phrases are used repeatedly throughout the claims: "directly or indirectly attached" and "modified or unmodified." These phrases are vague because

they do not specify the particular type of structural modification or attachment that fulfills the functional limitations.

The method claims 21 - 39 have the same vague and indefinite deficiencies as claims 1 - 20 but with additional problems The method of inhibiting RNA is indefinite because it does not specify the concentration of the inhibitor, the method of delivery(added to media or injected into cell, or location of the RNA (either intracellular or isolated).

Claim 40 is indefinite because it fails to specify the criteria for selecting the nucleotide compound having appropriate resistance to nuclease activity. There are no reaction conditions for the nuclease digestions and also no indication concerning the extent of digestion that establishes that a compound is or is not sufficiently resistant to function as an RNA inhibitor.

Claim 41 is vague for the same reasons that claim 1 and 21 are indefinite. Furthermore, there is no regimen, dosage and schedule, provided for treating a human or animal. The RNA to be inhibited is not specified either.

Claims 42 - 50 are even more vague and indefinite than claims 1 - 20 because of the functional language that is intended to supplant structural definition:

> "at least 1 exonuclease and endonuclease resistant component"
>
> "capable of specifically binding with a nucleic acid

sequence of interest to inhibit the function thereof"

"when complexed with a complementary RNA, confers RNAse H sensitivity upon the RNA"

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz whose telephone number is (703) 308-3995.

M.K.

Gary L. Kunz:glk
August 25, 1991

Johnnie R. Brown
JOHNNIE R. BROWN
SUPERVISORY PATENT EXAMINER
ART UNIT 183